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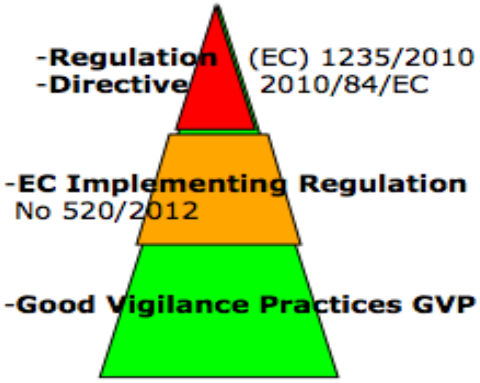
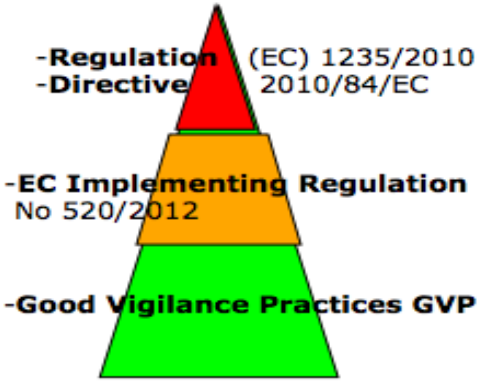
Signal management
November 8, 2012



Sabine Straus
Medicines Evaluation Board

- ✓ Introduction /context
- ✓ Signal detection in the new EU legislation
- ✓ GVP Module IX: Signal Management
- ✓ Practical aspects



6. Conclusion

This impact assessment has shown that increasing the clarity, efficiency and quality of the EU system of pharmacovigilance, through amendments to the existing EU legal framework, presents a win win situation with major public health improvements of at least 591 lives and €237 Million of public health burden saved per year across the EU and overall cost savings of €145 Million per year to the EU industry sector.

Historically, spontaneous reports have been the main source of postmarketing surveillance.

- Arnaiz JA, Carne X, Riba N, et al. The use of evidence in pharmacovigilance: case reports as th reference source for drug withdrawals.

Eur J Clin Pharmacol 2001; 57 (1): 89-91

- Lasser KE, Allen PD, Woolhandler SJ, et al. Timing of new black box warnings and withdrawals for prescription medications.

JAMA 2002; 287 (17): 2215-20

- Clarke A, Deeks JJ, Shakir SA. An assessment of the publicly disseminated evidence of safety used in decisions to withdraw medicinal products from the UK and US markets.

Drug Saf 2006; 29 (2): 175-81

- Olivier P, Montastruc JL. The nature of the scientific evi- dence leading to drug withdrawals for pharmacovigilance reasons in France.

Pharmacoepidemiol Drug Saf 2006; 15 (11): 808-12

INDEPTH: FAINT WARNING

From coloured tabs to computerized signals: How Canada tracks dangerous drugs

Paddy Moore | CBC News Online | February 17, 2004 (Updated Dec. 8, 2005)

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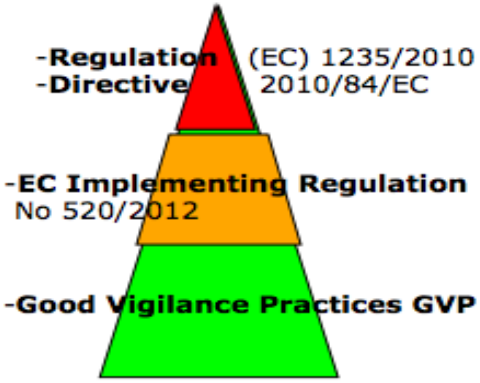

The new EU PV Legislation: four topic areas.

- **Collection of key information on medicines**
  Risk management plans
  Periodic safety update reports (PSURs)
  Post-authorisation safety and efficacy studies (PASS/PAES)
  Electronic submission of core medicine information by pharmaceutical industry
  Reporting by patients

- **Regulatory action to safeguard public health**
  Scientific committees and decision-making
  Strengthening referral procedures

- **Better analysis and understanding of data and information**
  EudraVigilance and signal detection
  Additional monitoring
  IT systems to support processing and analysis of data

- **Communication with stakeholders**
  Online publishing of information
  Coordination of safety messages
  Public hearings

A new Pharmacovigilance Risk Assessment Committee (PRAC) will focus on the planning, assessment and monitoring of safety issues. The CHMP will start to adopt opinions based on recommendations from the PRAC.

Article 28a

1. Regarding medicinal products for human use authorised in accordance with this Regulation, the Agency shall, in collaboration with the Member States, take the following measures:

(a) monitor the outcome of risk minimisation measures contained in risk management plans and of conditions referred to in points (c), (ca), (cb) and (cc) of Article 9(4) or in points (a) and (b) of Article 10a(1), and in Article 14(7) and (8);

(b) assess updates to the risk management system;

(c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance.

2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

3. The Agency and national competent authorities and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the risk-benefit balance being detected.

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2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

- Responsibility for Marketing Authorisation Holder (D104.3.e)
  monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit risk balance

- Responsibility for EMA and Member States (D107h)
  monitor the data in the EudraVigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk benefit balance'

Communication Art107h

3. The Agency and national competent authorities and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the risk-benefit balance being detected.

Member States shall ensure that marketing authorisation holders inform the Agency and national competent authorities in the event of new risks or risks that have changed or when changes to the risk-benefit balance have been detected.

20.6.2012 EN Official Journal of the European Union L 159/5

COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012

of 19 June 2012

on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council

(Text with EEA relevance)

CHAPTER III

Minimum requirements for the monitoring of data in the Eudravigilance database

Implementing Regulation

CHAPTER III

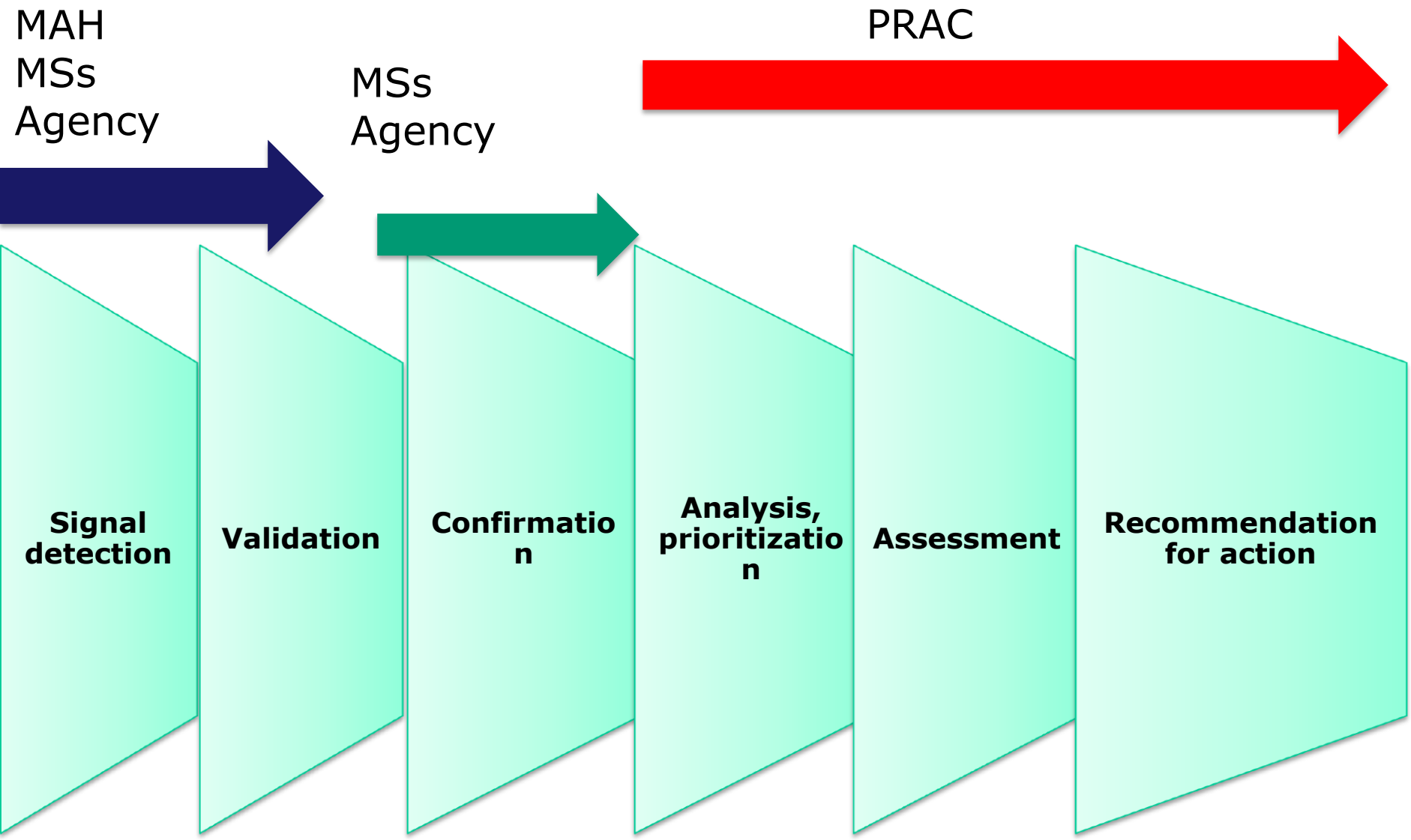
Minimum requirements for the monitoring of data in the Eudravigilance database

Article 18

General requirements

Art 18 –General requirements
Art 19 - Changed/new risks
Art 20 - Methodology
Art 21 - Signal management process
Art 22 - Work sharing for signal management
Art 23 - Signal detection support
Art 24 - Signal detection audit trail

Signal Management Process IR art 21



Signal management

Article 21

Signal management process

1. The signal management process shall include the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment, and recommendation for action.

For the purposes of this Article, 'signal validation' means the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

Validation by MAH

If the MAH detects a new signal when monitoring the Eudravigilance database, it shall validate it and shall forthwith inform the Agency and national competent authorities.

Validation by NCA and the Agency

When analysing the validated signal, national competent authorities and the Agency may take into account other information available on the medicinal product.

if validity not confirmed, special attention shall be paid to non-confirmed signals concerning a medicinal product where those signals are subsequently followed by new signals concerning the same medicinal product.

validate and confirm any signal that they have detected during their continuous monitoring of the Eudravigilance database

Confirmation

Responsibility

AGENCY → Signal concerns a product authorised in accordance with Regulation (EC) No 726/2004

(Lead) MEMBER STATE → Signal concerns a product authorised in accordance with Directive 2001/83/EC

Signal analysis, prioritisation and assessment by the Pharmacovigilance Risk Assessment Committee (PRAC)

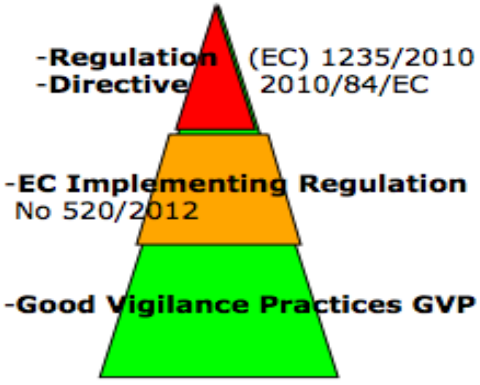
Urgent action required before the next PRAC meeting:

Rapid Alert procedure

All other signals:

Sent to the PRAC for consideration at its next meeting.

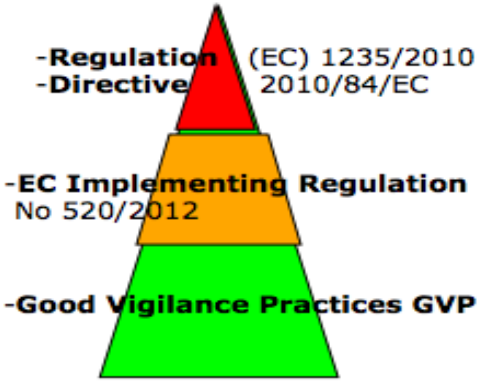
- ✓ Introduction /context
- ✓ Signal detection in the new EU legislation
- ✓ GVP Module IX: Signal Management
- ✓ Practical aspects



Roles and responsibilities of stakeholders (GVP IX)

- **Roles and responsibilities of the Agency**
- **Roles and responsibilities of the lead Member State**
- **Roles and responsibilities of the national competent authorities**
- **Roles and responsibilities of the Pharmacovigilance Risk Assessment Committee**
- **Roles and responsibilities of marketing authorisation holder**

- ✓ Introduction /context
- ✓ Signal detection in the new EU legislation
- ✓ GVP Module IX: Signal Management
- ✓ PRACtical aspects



Roles and responsibilities of the PRAC

Signal management

- shall prioritise validated and confirmed signals for further assessment
- nominate a Rapporteur for the assessment of the validated and confirmed signals with a time frame for the assessment
- transmit to the CHMP/CMDh any recommendations for action following the signal assessment

Methodology

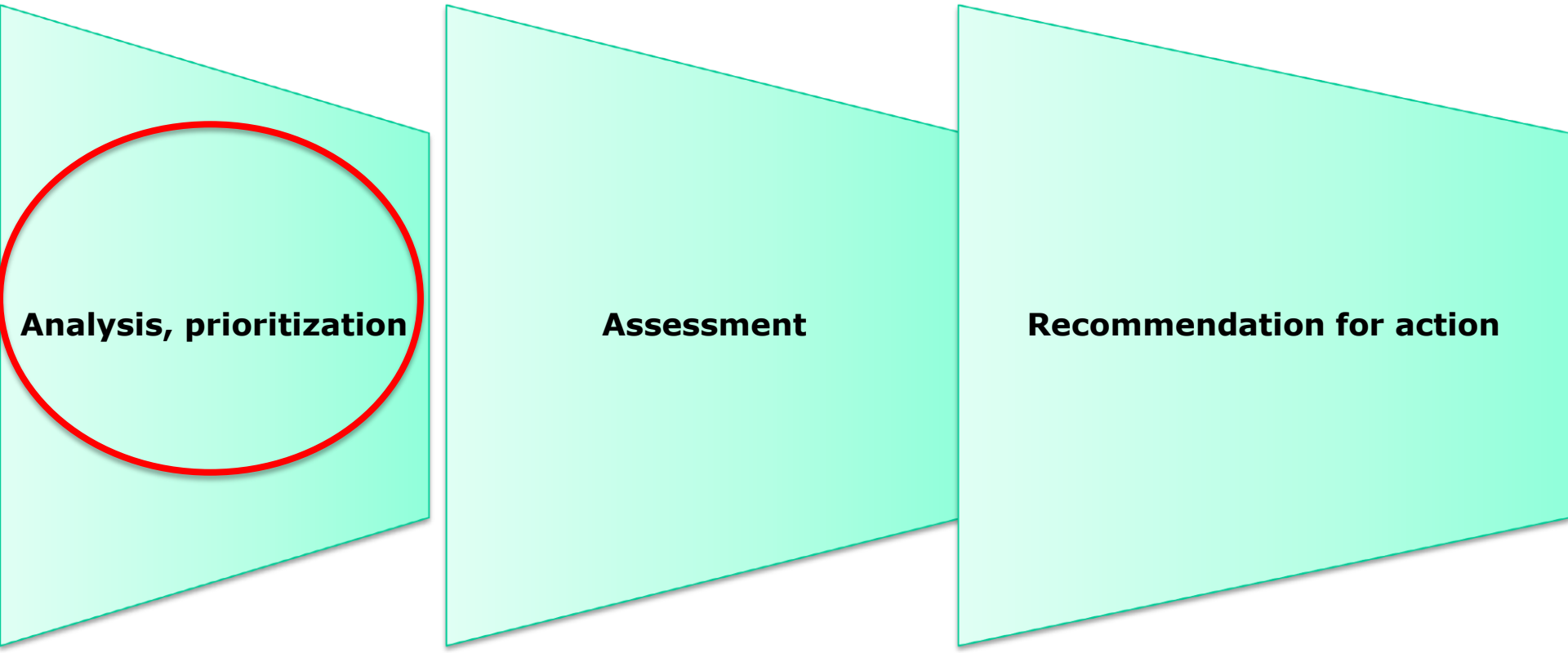
- Regular review of the signal management methodology to be used
- publish recommendations as appropriate

Review

- at least every 4 years the (co)lead Member States responsible for the monitoring the data in EudraVigilance
- list of medical events that have to be taken into account

Signal Management Process IR art 21

PRAC



1 st step in the PRAC
Signal analysis and prioritisation

Signal Confirmation in EPITT

Agenda PRAC

- Discussion in plenary by lead MS + analysis and proposal for action
- Agreemend at plenary
- Recommendation adopted

EMA to communicate to MAHs
Minutes of the PRAC at EMA web site

Recommendation: action requested and time table

Urgent action

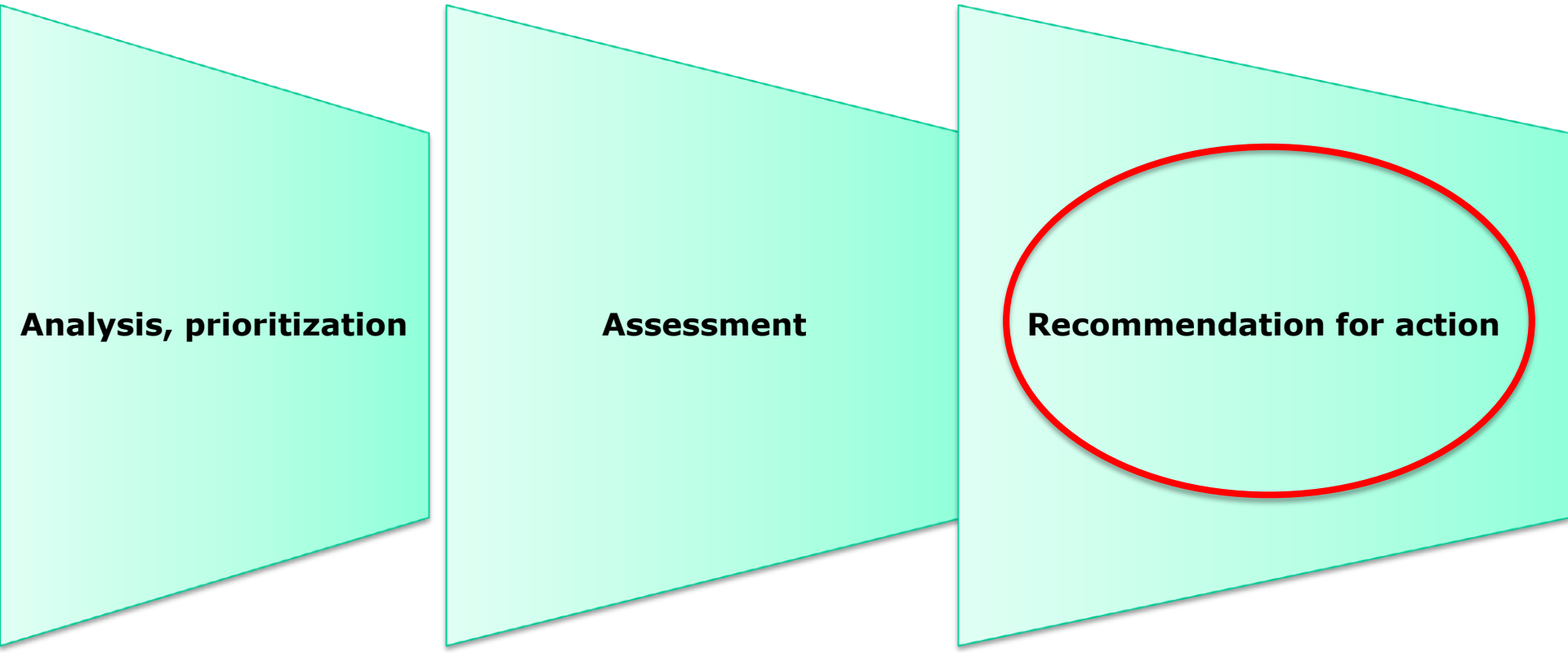
No regulatory action

Further action required

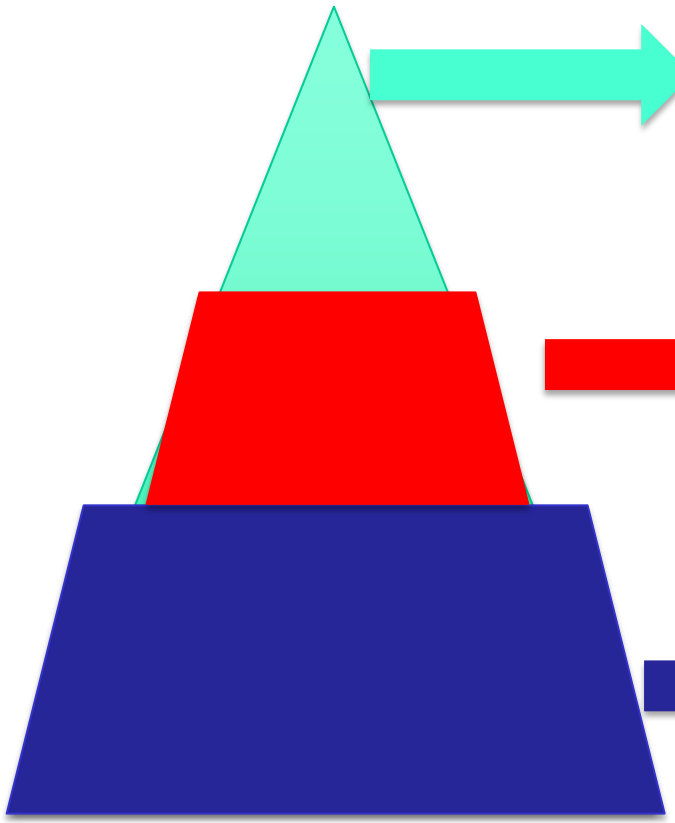
Recommendation made public : minutes PRAC

Signal Management Process IR art 21

PRAC



PRAC : recommendation to the CHMP or to the CMDh, as appropriate Fproposal for action following the signal assessment including time table



Suspension
Revocation
Urgent safety restriction

Pro active actions: study, RMP additional risk minimisation

SPC amendment

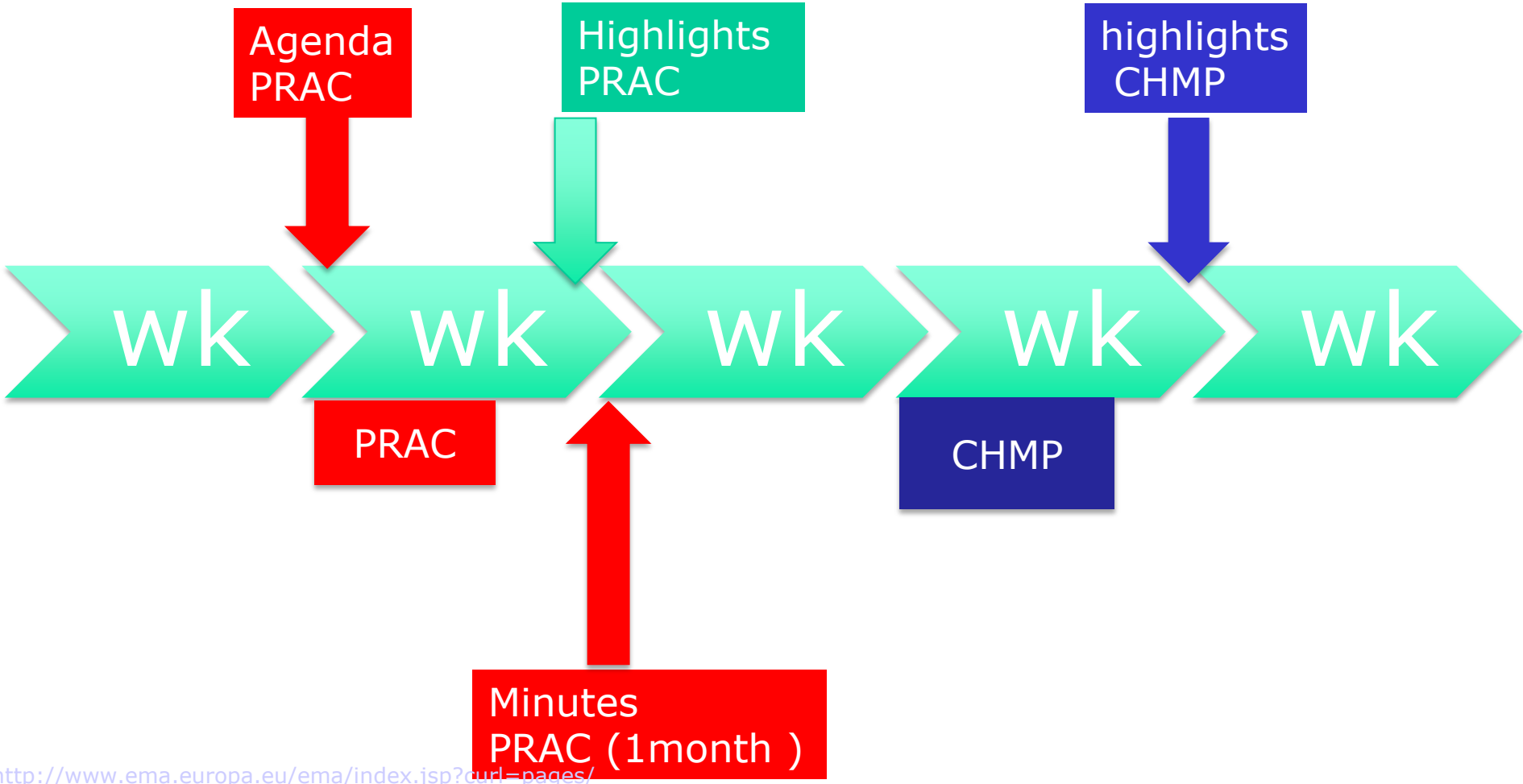
No action

Additonal data to be collected

PRAC output recommendation

'For the fulfilment of its pharmacovigilance tasks, including the approval of risk management systems and monitoring their effectiveness provided for under this Regulation, the Committee for Medicinal Products for Human Use shall rely on the scientific assessment and recommendations of the Pharmacovigilance Risk Assessment Committee referred to in Article 56(1)(aa).';

For the fulfilment of its pharmacovigilance tasks, including approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee provided for in Article 56(1)(aa) of Regulation (EC) No 726/2004.



http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing000353.jsp&mid=WC0b01ac05805a21cf

Agendas

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Document(s)	Language	Status	First published	Last updated	Effective Date
Agenda - PRAC draft agenda of meeting 29-31 October 2012	(English only)	draft	29/10/2012		
Agenda - PRAC draft agenda of meeting 1-3 October 2012	(English only)	draft	01/10/2012		
Agenda - PRAC draft agenda of meeting 3-5 September 2012	(English only)	draft	03/09/2012		
Agenda - PRAC draft agenda of the inaugural plenary meeting 19-20 July 2012	(English only)	draft	18/07/2012		

Document(s)	Language	Status	First published
Minutes - PRAC meeting 1-3 October 2012	(English only)	adopted	07/11/2012
Minutes - PRAC meeting 3-5 September 2012	(English only)	adopted	05/10/2012
Minutes - PRAC inaugural plenary meeting 19-20 July 2012	(English only)		07/09/2012

4. Signals assessment and prioritisation

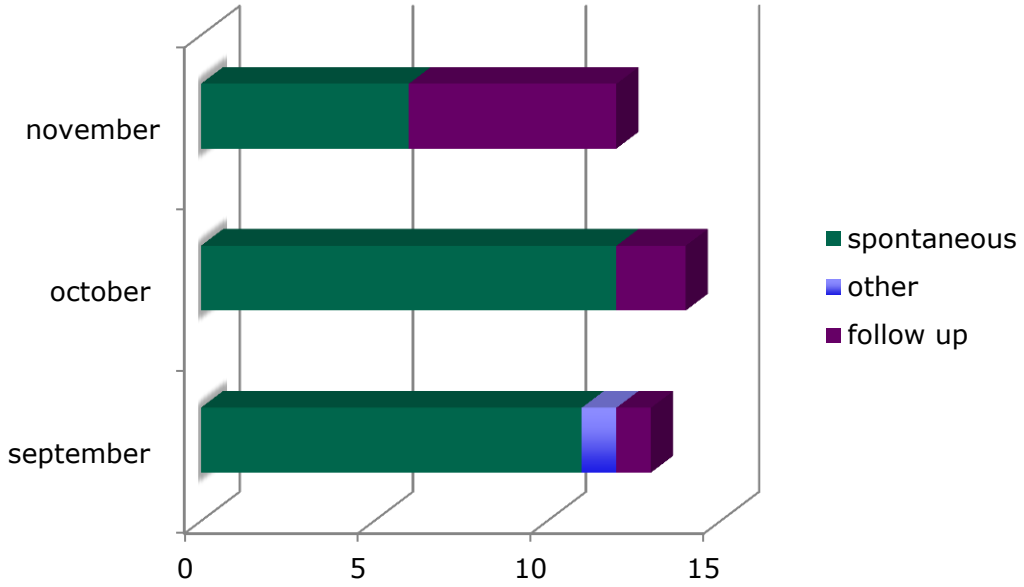
4.1. New signals detected from EU spontaneous reporting systems

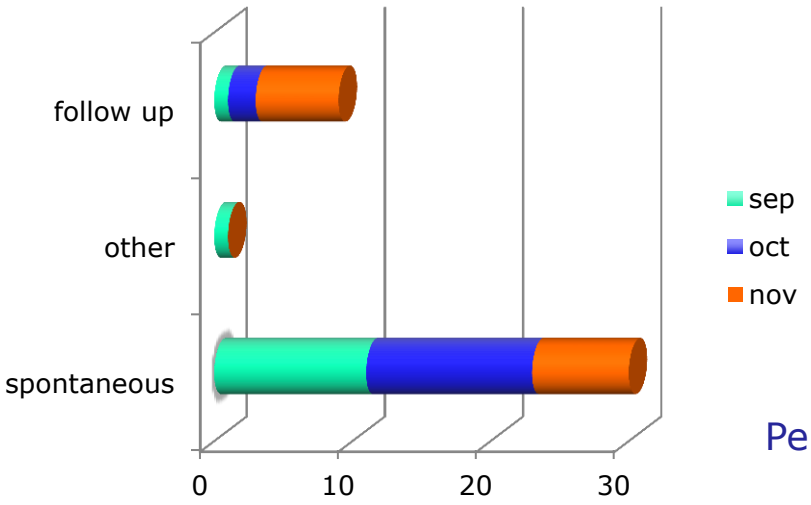
4.2. New signals detected from other sources

4.3. Signals follow-up and prioritisation

Signals on the PRAC agenda

Per month





Per item

4. Signals assessment and prioritisation

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Adalimumab – HUMIRA** (CAP)

- Signal of dermatomyositis

Status: *for initial discussion*

Regulatory details:

PRAC Rapporteur: Ulla Wändel-Liminga (SE)

4.1.2. Cinacalcet – MIMPARA (CAP)

- Signal of QT prolongation/ventricular arrhythmias

Status: *for initial discussion*

Regulatory details:

Recommendation(s)

- The Marketing Authorisation Holder (MAH) for Humira (adalimumab) and MAH for Remicade (infliximab) should submit within 30 days a cumulative review of dermatomyositis, discuss plausible pathophysiologic mechanisms and consider labelling change. A 60 day-assessment timetable was supported to assess the results of this review, leading to a further PRAC recommendation.

The EMA will review cases of dermatomyositis reported to EudraVigilance in association with pharmacologically related substances and report back to the PRAC.

4.1.8. **Somatropin** – NUTROPINAQ, OMNITROPE (CAPs, NAPs)

- Signal of convulsions (SMQs – Standardised MedDRA Queries)

Discussion

The PRAC discussed the information arising from the review of the cases, describing reactions falling under the category of convulsions. The PRAC reflected on the fact that a number of literature articles described a potential association between somatropin and convulsions and that the product information of some somatropins already lists raised intracranial pressure as an adverse effect. However, the PRAC agreed that the signal warranted further investigation with a view to strengthening risk minimisation as appropriate.

Recommendation(s)

The Committee appointed Sabine Straus (NL) as PRAC Rapporteur.

- The MAHs for all authorised products should be requested to perform within 120 days a cumulative review of case reports from all sources and available - literature of 'SMQ Narrow (Standardised MedDRA Queries, narrow scope) Convulsions' associated with somatropin. A 60 day-timetable was supported to assess the results of this review leading to a further PRAC recommendation.

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